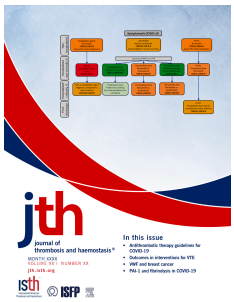
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



COVID-19 outcomes in persons with hemophilia: results from a US-based national COVID-19 surveillance registry

Anjali Sharathkumar, Linder Wendt, Chris Ortman, Ragha Srinivasan, Christopher Chute, Elizabeth Chrischilles, Clifford Takemoto, for the National COVID Cohort Collaborative Consortium

PII: S1538-7836(23)00401-4

DOI: https://doi.org/10.1016/j.jtha.2023.04.040

Reference: JTHA 270

To appear in: *Journal of Thrombosis and Haemostasis*

Received Date: 9 February 2023

Revised Date: 29 March 2023

Accepted Date: 25 April 2023

Please cite this article as: Sharathkumar A, Wendt L, Ortman C, Srinivasan R, Chute C, Chrischilles E, Takemoto C, for the National COVID Cohort Collaborative Consortium, COVID-19 outcomes in persons with hemophilia: results from a US-based national COVID-19 surveillance registry, *Journal of Thrombosis and Haemostasis* (2023), doi: https://doi.org/10.1016/j.jtha.2023.04.040.

Title:

COVID-19 outcomes in persons with hemophilia: results from a US-based national COVID-19 surveillance registry

Anjali Sharathkumar[1], Linder Wendt[2], Chris Ortman[3,4], Ragha Srinivasan[4], Christopher Chute[5]; Elizabeth Chrischilles[3,6,] Clifford Takemoto[4] for the National COVID Cohort Collaborative Consortium

[1] Stead family Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA

[2] Institute for Clinical and Translational Science, University of Iowa, Iowa City, IA

[3] Department of Bioinformatics, University of Iowa, Iowa City, IA

[4] Department of Hematology, St. Jude Children's Research Hospital, Memphis

[5] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[6] Department of Epidemiology, School of Public Health, University of Iowa, IA

Running title: Hemophilia and COVID-19 outcomes

Key words: COVID-19; hemophilia; health outcomes; venous thromboembolism; mortality

Word count: Abstract, 250; Main article, 4444

Tables: 4; Figures: 3; Supplementary Appendix: 1

Corresponding author:

Anjali Sharathkumar, MD

200 Hawkins Drive, Iowa City Iowa, IA, USA. 52242

Phone: 319 356 1616/ Cell: 317 730 4334/ Fax: 319 356 7656

Email: anjali-sharathumar@uiowa.edu

Essentials

- Hemophilia did not offer protection against COVID-19 severity or mortality.
- Hemophilia did not reduce the VTE risk but increased the bleeding risk with COVID-19.
- Older age, chronic medical conditions, and bleeding history adversely affected outcomes in PwH.
- Pre-COVID VTE events and anticoagulation increased VTE risk with COVID-19 in PwH.

Abstract

Introduction: Hypercoagulable state contributing to thrombotic complications worsens COVID-19 severity and outcomes, while anticoagulation improves outcomes by alleviating hypercoagulability. **Objectives:** Examine whether hemophilia, an inherent hypocoagulable condition, offers protection against COVID-19 severity and reduces VTE risk in persons with hemophilia (PwH). **Patients/Methods:** A 1: 3 propensity score (PS) matched retrospective cohort study used national COVID-19 registry data (January 2020 through January 2022) to compare outcomes between 300 male PwH and 900 matched controls without hemophilia. **Results:** Analyses of PwH demonstrated known risk-factors (older age, heart failure, hypertension, cancer/malignancy, dementia, renal and liver disease) contributed to severe COVID-19 and/or 30-day-all-cause mortality. Non-CNS bleeding was an additional risk-factor for poor outcomes in PwH. Odds of developing VTE with COVID-19 in PwH were associated with pre-COVID VTE diagnosis (OR 51.9, 95% CI 12.8-266, p<0.001), anticoagulation therapy (OR 12.7, 95% CI 3.01-48.6, p<0.001) and pulmonary disease (OR 16.1, 95% CI 10.4-25.4, p<0.001). Thirty-day-all-cause-mortality (OR 1.27, 95% CI 0.75-2.11, p=0.3), and VTE events (OR 1.32, 95% CI 0.64-2.73, p=0.4) were not significantly different between matched cohorts; however, hospitalizations (OR 1.58, 95% CI 1.20-2.10, p 0.001) and non-CNS bleeding events (OR 4.78, 95% CI 2.98-7.48, p<0.001) were increased in PwH. In multivariate analyses, hemophilia did not reduce adverse outcomes (OR 1.32, 95% CI 0.74-2.31, p 0.2) nor VTE (OR 1.14; 95% CI 0.44-2.67, p 0.8) but increased bleeding risk (OR 4.70, 95% CI 2.98-7.48, p<0.001). **Conclusion:** After adjusting for patient characteristics/comorbidities, hemophilia increased bleeding risk with COVID-19 but did not protect against severe disease and VTE.

Keywords: COVID-19; Hemophilia; VTE, mortality, outcomes

Abbreviations: Factor: F; PwH: Persons with hemophilia; COVID-19: Corona Virus Disease-19; ICU: Intensive care unit; CNS: central nervous system; DVT: deep venous thrombosis; VTE: venous thromboembolism; PE: pulmonary embolism; PS: propensity score; F: factor; N3C: National COVID cohort collaborative; WHO: World health organization; OMOP: Observational Medical Outcomes Partnership; ICU: Intensive care unit

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 infection, has disproportionately affected people with chronic medical conditions.[1-3] An acquired hypercoagulable state plays a pivotal role in pathogenesis and severity of COVID-19.[4] Consequently, conditions associated with underlying hypercoagulability including older age, cardiovascular disease, renal or liver disease, cancer, pulmonary disease increase the risk of severe COVID-19 by six to eight-fold.[1, 2, 5-12] Clinical manifestations of hypercoagulability include venous thromboembolism (VTE), encompassing deep venous thrombosis (DVT) or pulmonary embolism (PE), and microvascular thrombosis contributing to multi-organ failure.[1, 2, 13, 14] VTE is diagnosed in up to 30% of patients which in turn is associated with adverse outcomes in up to 50% of patients with severe COVID-19.[13, 14] Anticoagulation therapy reduces the mortality in patients hospitalized with COVID-19, potentially through alleviating the hypercoagulable state and thrombogenesis.[15] Therefore, thromboprophylaxis with anticoagulation remains the standard-of-care for patients hospitalized with COVID-19.[16, 17]

The association between hypercoagulability and COVID-19 severity raises a critical question whether the hypocoagulable state in patients with inherited coagulation factor deficiencies such as hemophilia A (factor VIII deficiency) and B (factor IX deficiency) offers biologic protection against COVID-19 severity.[18] Hemophilia is a rare but serious bleeding disorder affecting ~30,000 males in United States (US).[19] The literature about outcomes of COVID-19 in persons with hemophilia (PwH) is sparce and limited to registry data[20], case series[21, 22], case reports [22-25] and expert opinion.[26] Although several reports suggest that the clinical course of COVID-19 is relatively mild in PwH, they are limited by lack of comparator groups, non-hypothesis-driven analyses, and reporting bias; thus, accurate assessments of risk-factors and outcomes of COVID-19 in PwH is limited.

To address this knowledge gap, we conducted an epidemiological study to examine risk-factors and outcomes of COVID-19 in PwH with specific focus on VTE and bleeding risks. We hypothesized that, given that many comorbidities associated with a hypercoagulable tendency, and the role of thrombogenesis in the development of severe COVID-19 as well as the beneficial effect of

anticoagulation in hospitalized patients – the hypocoagulable state of hemophilia offers a relative benefit against COVID-19 severity. We designed a propensity-score (PS) matched cohort study to investigate whether hemophilia as an exposure offers biologic protection against COVID-19 severity.[27] We used a data-driven approach and leveraged the national surveillance system-National COVID Cohort Collaborative (N3C)- that was implemented to follow trends and outcomes of COVID-19 in United States (US).[1, 28] As of January 2022, the N3C Registry, commonly known as N3C Data Enclave, contained more than 100 million unique subjects including ~10 million cases of COVID-19. This large sample size provided an opportunity to address our research questions for a rare disease like hemophilia and generate clinically meaningful results.

2 | STUDY DESIGN AND METHODS

2.1 | Study design and data Source

This 1:3 (cases to controls) PS-matched retrospective observational cohort study included COVID-19 cases with hemophilia and PS-matched controls without hemophilia. Study cohorts were identified from the N3C Data enclave whose data was released for research as of January 31st, 2022. The N3C enclave is a centralized, harmonized, high quality, high-granularity electronic health record repository of COVID-19 cases and controls. The data is pulled from 75+ healthcare facilities across US from a wide geographic distribution and contains patients who have had SARS-CoV-2 testing with a diagnosis of COVID-19. (Supplementary Appendix A).[1, 28, 29] The participating sites enter all laboratory-confirmed, suspected or confirmed, cases with COVID-19 diagnosis as well as controls (no age or demographic restriction) who have tested negative/equivocal for SARS-CoV-2 test results at a ratio of 1:2 (case: controls). For each patient, the cohort entry date is the date of the first SARS-CoV-2 test. The N3C enclave uses the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) to harmonize the data from disparate coding systems with minimal information loss to a standardized vocabulary mapping source concepts from different systems (e.g., ICD-9, ICD-10, RxNorm, CPT4, NDC, etc.).[30, 31] Site data that pass a robust data quality assessment pipeline are integrated into the "release" set for use by the community.[32]

Details about the data transfer, harmonization, quality, and integration processes have been previously published (Supplementary Appendix A).[28]

2.2 | COVID-19 case definition

A COVID-19 case is defined as a patient with positive SARS-CoV-2 test result (either by real-time RT-PCR assay of nasal or pharyngeal swabs and/or serology testing) with one or more ICD-10 or SNOMED diagnostic codes for COVID-19 during the same encounter or on the same date prior to 01/31/2022 (Supplementary Appendix, B). N3C Enclave also includes historical patient data (lookback data) from the same health-care system as of January 1st, 2018 (prior to the first diagnosed case of COVID-19 in the US). These data provide information about pre-existing comorbidities (Supplementary Table S1) and other medical history on study subjects. The cohort definitions and analytic pipelines developed for defining cohort phenotypes (demographic, clinical, laboratory) are publicly available at GitHub.[33]

2.3 | Identification of hemophilia cohort

Since hemophilia A and B affects primarily males, the study included only male subjects with hemophilia. The hemophilia cohort was identified by defining a hemophilia concept set (Supplementary Appendix C) using standard OMOP concepts for hemophilia ICD-10 diagnosis codes (hemophilia A/hereditary FVIII deficiency [D66], hemophilia B/ hereditary FIX deficiency[D67]). Additional diagnoses of hemophilic arthropathy (D36.2), and hemophilia therapeutics (J-codes) were included to confirm hemophilia diagnosis. Exclusion criteria included lack of documentation of SARS-CoV-2 test results, and an incorrect hemophilia diagnosis through data review.

2.4 | Patient variables

Patient-level variables extracted from N3C domain tables included demography (age, sex, race/ethnicity, insurance), pre-existing organ comorbidities (cardiovascular, pulmonary, dementia), substance abuse, tobacco smoking, VTE and anticoagulant use) and hemophilia-related variables (renal disease, bleeding comorbidity, hepatitis C and HIV, hemophilia therapeutics) (Table 1).[18, 34, 35] Previously validated OMOP concept sets for N3C cohort were used for defining demographic variables, comorbid conditions, and outcomes (Supplementary Appendix Table S1).[1, 28, 36] Bleeding comorbidity was categorized as hemarthrosis/joint bleeding, CNS-, and non-CNS bleeding. Non-CNS bleeding was limited to soft tissue and organ bleeding outside CNS and joint. New concept sets were developed for categorizing bleeding comorbidities.

2.5 | Identification of PS-matched non-hemophilia cohort

PS-matching variables included demography and following chronic medical comorbidities: cardiac, cerebrovascular, diabetes, dementia, cancer, pulmonary, liver disease, rheumatology, substance abuse, and smoking (Supplementary Appendix S2; Table 1). The variables associated with hemophilia-specific comorbidities and thrombosis - CNS and non-CNS bleeding, hemarthrosis, renal disease, HIV and hepatitis C, hemophilia therapy, VTE and anticoagulation therapy- were not included for PS-matching.[18, 34, 35, 37, 38]

2.6 | Hospital Index Encounter for COVID-19 positive patients

The term “Index encounter” is the longest encounter associated with a COVID-19 diagnosis that met the case definition described in section 2.3.[1, 33] The cohort was limited to all patients who had their earliest SARS-CoV-2 positive test date within 30-days before the start of the index encounter and up to 7-days after the start of the index encounter. Among multiple recorded encounters per patient including ambulatory visits, emergency room visits, inpatient hospitalizations, the longest encounter within the timeframe for COVID-19 was selected. If the patient was recorded as deceased, the most recent visit was selected.

2.7 | Outcome variables

Outcomes were analyzed from the beginning of index encounter through 30-days after the end of index encounter. The primary adverse outcomes were severe COVID-19[39] and/or 30-day-all-cause mortality for COVID-19 positive patients. COVID-19 disease severity was assessed using the Clinical Progression Scale designed by WHO (Supplementary Appendix D).[39] Disease severity was assessed as mild, moderate or severe. Ambulatory encounters or encounters <48 hours were considered mild while hospitalization was considered as "moderate to severe" disease depending on the amount of supplemental oxygen, type of ventilatory support and life-saving interventions. The maximum severity documented during patient-specific index encounter was used to assign the severity. Mortality was defined by documentation of death or discharge to hospice.[1, 28, 33]

Other outcomes included indicators of clinical severity: rates and duration of hospitalization and ICU admission, hypoxia (oxygen saturation<90%), use of mechanical ventilation and extracorporeal membrane oxygenation (ECMO), rates of VTE and bleeding diathesis (CNS-and non-CNS hemorrhage). Hospitalization was defined as a single index encounter for each laboratory-confirmed positive patient visit that spanned at least three calendar days. ICU admission was defined as use of life-supportive interventions like requirement of high flow oxygen, or invasive ventilation and or other interventions like ECMO.

2.8 | Institutional Review Board (IRB) approval

The N3C Data Enclave is approved under the authority of the National Institute of Health Review Board (#IRB00249128). The N3C data access committee approved the deidentified (Level II) data use request for our project (RP-6A939B). This study was not considered human subject research by University of Iowa IRB.

3 | STATISTICAL ANALYSES

The logistic regression framework was used to examine associations between hemophilia and COVID-19 adverse outcomes. To minimize confounding and other sources of bias arising from the use of observational data, a propensity model was constructed to match hemophilia patients and controls without hemophilia at a 1:3 ratio. Propensity scores were calculated based on the characteristics listed in Table 1 (demographic variables, comorbidities unrelated to hemophilia), and matching was based on the greedy nearest neighbor matching algorithm with a caliper of 0.1 pooled standard deviations.[40, 41] The matching procedure ensured that the comparison groups were similar in demography and distribution of clinical comorbidities so that attributable risk of hemophilia could be estimated.

Summary statistics were calculated for demographic and clinical measures stratified by cohort. Continuous measures were presented as medians (interquartile ranges, IQR) and categorical measures were presented as counts (percentages). Differences between cohorts were assessed using Wilcoxon rank sum and Fisher's Exact tests for continuous and categorical variables, respectively. Univariate logistic models were fit to assess the relationships of all demographic and clinical measures and severe or fatal COVID-19. Subsequently, multivariate model selection was conducted using a forward stepwise approach based on AIC (Akaike information criterion) to identify the optimal predictor set associated with severe or fatal COVID-19. Models were also constructed with the purpose of examining the impact of anticoagulation on VTE during the COVID-19 index encounter and bleeding during the COVID-19 index encounter and how that impact may differ between persons with and without hemophilia. An interaction term between anticoagulant use and hemophilia status was used in these models to assess whether anticoagulant use had a different effect on each outcome variable when it was used by PwH. Odds ratios point estimates, and 95% confidence intervals were reported for all univariate and multivariate modeling predictors along with p-values. Additional sub-group analyses were performed to assess the risk factors for VTE and bleeding during index encounter. Given multiple outcomes of interest, we considered a more stringent two-sided alpha of 0.01 to determine statistical significance for differences in outcome rates.

3.1 | Sample size justification

With a sample of 300 PwH and 900 matched controls, if we assume a 20% event rate in our controls and we employ our statistical significance threshold of 0.01, we have 94.4% power to detect a difference between our groups if the true event rate in our PwH is 10%.

The N3C Download committee reviewed and granted an appeal for this manuscript to report cell numbers as low as 10 (instead of the normal threshold of 20) due to rarity of hemophilia. Cell count <10 was not reported to protect the privacy of individuals. All analyses were performed within the N3C Data Enclave on the Palantir platform.

4 | RESULTS

4.1 | Cohort characteristics and outcomes

From the cohort of 1,676 PwH identified from the dataset of 4,094,889 males, a total of 300 PwH diagnosed with COVID-19 were included in the study (Figure 1). There were 235 (78%) patients with Hemophilia A, 46 (15%) with Hemophilia B, while the remaining 19 (6.3%) were categorized as hemophilia unspecified as they had a diagnosis code for both hemophilia A and B. Eight patients (hemophilia A, 6; hemophilia B, 2) had inhibitors (antibodies against factor VIII or IX). We constructed a PS-matched cohort of 900 patients without hemophilia (section 2.5). The demographic and clinical characteristics for each cohort are shown in Table 1. The study population was 60% white, and insurance status was unknown in 75%. A majority were overweight or obese (70%). Hypertension was the most common comorbidity (40%), while only 18% of the cohort had a Charlson comorbidity index (CCI) of >5.[42]

4.1.1 | Comparison of COVID-19 patient characteristics between PwH and those without hemophilia

As expected, hemophilia related unmatched comorbidities- hepatitis C, CNS- and non-CNS bleeding events, hemarthrosis, hemophilia therapy - were significantly higher in PwH, ($p<0.001$) except renal disease. The risk of renal comorbidity was significantly lower in hemophilia cohort compared to the non-hemophilia controls. Only 10% (n=30) of PwH received hemophilia specific therapies. A higher proportion of PwH had history of VTE, 6.9% (n=20) compared to 4% (n=35) in the non-hemophilia cohort and only 5.7%, (n=17) of PwH were on anticoagulation therapy compared to

8.3% (n=75) without hemophilia prior to the COVID-19 diagnosis (p>0.2). A similar proportion of PwH and those without hemophilia, (15%, n=45 versus 16%, n=147; p=0.2), received anticoagulation therapy during the index encounter, primarily with heparins.

4.1.2 | Comparison of COVID-19 outcomes between PwH and those without hemophilia

We compared the clinical outcomes between PwH and PS-matched controls (Table 2). The majority of COVID-19 outcomes were similar between hemophilia and non-hemophilia cohorts (Table 2). PwH were more likely to have moderate severity of COVID-19 compared to the non-hemophilia cohort (OR, 1.58, 95% CI 1.14 to 2.18, p=0.004). But only a small proportion had severe COVID-19 in each cohort (<3% each). The 30-day-all-cause mortality was 1.33 times higher among PwH compared to non-hemophilia cohort (5.7 vs. 4.3%), but this difference was not statistically significant (OR 1.26; 95% CI, 0.86 to 1.81, p=0.2). Hospitalization rates were significantly higher among PwH compared to those without (OR, 1.59; 95% CI, 1.20 to 2.10, p=0.001), but ICU admission rates were similar between the cohorts (<3.0% versus 3.1%). PwH experienced longer durations of ICU stay, but this was not statistically significant (median, 34-days versus 18-days, p=0.074). Non-CNS bleeding events were higher among PwH (OR, 3.74; 95% CI, 2.46 to 5.71, p<0.001), yet the rates of index VTE were similar between the two cohorts (OR, 1.28; 95% CI, 0.56 to 2.72, p=0.4). There were no notable differences between the rates of hypoxemia, invasive ventilation, and ECMO between PwH and their matched controls as shown in Table 2.

4.2 | Analyses of hemophilia cohort for risk-factor assessment

4.2.1 | Risk factors for adverse outcomes in PwH during COVID-19 index encounter

We constructed univariate models using only the hemophilia cohort to identify risk factors for adverse outcomes and found that older age (OR 1.04, 95% CI 1.01-1.07; p<0.001), heart failure (OR, 6.72, 95% CI 2.46 to 17.4; p<0.001), advanced liver disease (OR 6.36, 95% 2.05 to 18.2, p <0.001), dementia (OR 7.36, 95% CI 1.44 to 32.1; p=0.009), hypertension (OR 3.42, 95% CI 1.49 to 8.37; p=0.005), malignancy (OR 4.71, 95 CI 1.77 to 11.8; p=0.001), renal disease (95% CI 5.55, 95% CI 1.95 to14.7; p<0.001) were significant risk factors (Figure 2, Supplementary Table S6). However

other factors that have been identified in the general population, such as cerebrovascular disease or diabetes, were not found to be a significant risk factors for severe outcomes in PwH.

4.2.2 | Risk factors for VTE in PwH during COVID-19 index encounter

The subset analyses were performed to identify risk factors for VTE in PwH during index encounter. A previous history of VTE and/or anticoagulation use were associated with an increased risk of VTE during index encounter, [OR 51.9 (95% CI 12.8 – 266, p<0.001) and OR 12.7 (95% CI 3.01-48.6, p<0.001), respectively] (Figure 3 A; Supplementary Table S7, S8). Additionally, preexisting pulmonary disease was also shown to be associated with index-VTE (OR 5.00, 95% CI 1.5-17.9, p = 0.01).

4.2.3 | Risk factors for bleeding in PwH during COVID-19 index encounter

The subset analyses to identify risk factors for bleeding showed that the odds of bleeding events (CNS- and non-CNS) with COVID-19 were increased by the presence of moderate liver disease (OR 4.37, 95% CI 1.65-11.4; p=0.002), tobacco smoking (OR 4.10, 95% CI 1.64-10.1; p=0.002), hepatitis C (OR 2.88, 95% CI 1.41-5.73), non-CNS bleeding before COVID-19 (OR 6.87, 95% CI 3.69-13.3; p=0.003), and hemarthrosis (OR 3.41, 95% CI 1.7-6.7; <0.001) (Figure 3B; Supplementary Table S7, S9).

4.3 | Analyses of PS-matched cohorts for risk factor assessment

4.3.1 | Risk factors for COVID-19 adverse outcomes in the PS-matched cohort during COVID-19 index encounter

In the univariate model, multiple previously identified comorbidities - older age, cardiovascular disease, cerebrovascular disease, liver disease, pulmonary disease, bleeding, smoking, VTE, anticoagulation- significantly increased the odds of adverse outcomes for the entire cohort.

However, the diagnosis of hemophilia was not associated with severe disease (Supplementary Table S2). Similarly, in the multivariate models, participants' hemophilia status did not significantly influence COVID-19 adverse outcomes (OR, 1.32; 95% CI 0.74 to 2.31, p=0.3; Table 3). However, older age, heart failure, moderate liver disease, and CNS-bleeding significantly increased the odds of adverse outcomes by 1.03 (95% CI, 1.02 to 1.05; p<0.001), 3.53 (95% CI 1.97 to 6.31; p<0.001), 7.05 (95 CI, 3.69 to 13.4; p<0.001), 5.39 (95% CI, 1.70 to 16.0; p=0.003) respectively.

4.3.2 | Risk factors for VTE in the PS-matched cohort during COVID-19 index encounter

The univariate analyses for VTE risk factors in the entire PS-matched cohort showed that older age, coronary artery disease, diabetes with complications, hypertension, history of VTE, and previous anticoagulation use were associated with increased odds for VTE for both PwH and non-hemophilia patients [Supplementary Table S3, S4]. In the multivariate model, older age (1.02, 95% CI 1.01 to 1.04; p=0.002) and pre-index anticoagulation use (3.95, 95% CI 1.54 to 9.37; <0.001) significantly increased the odds of developing index VTE (Table 4). The interaction term between anticoagulant use and hemophilia was not statistically significant (OR 0.56, 95% CI 0.04 to 6.98; p=0.6), meaning that among our study population, the risk of developing index VTE that was associated with prior anticoagulant use was similar whether a person had hemophilia or not.

4.3.3 | Risk factors for bleeding in the PS-matched cohort during COVID-19 index encounter

Univariate analyses of CNS and non-CNS bleeding outcome for the entire PS-matched cohort showed that hemophilia A, older age, heart failure, cerebrovascular disease, diabetes with complications, coronary disease, liver disease, malignancy, renal disease, substance abuse, tobacco smoking, pre-index anticoagulation use, HIV and hepatitis C, and history of bleeding increased the odds of bleeding by 1.02 to 11-fold (Supplementary Table S3, S5). In a multivariate analysis, hemophilia and liver disease significantly increased the odds for bleeding events, 4.70 (95% CI 2.98 to 7.48; p<0.001) and 4.26 (95% CI, 2.07 to 8.85; p<0.001) respectively (Table 4).

5 | Discussion

This is the first study from US to evaluate outcomes of COVID-19 in PwH compared to those without hemophilia from a large COVID-19 database. Our study addressed the question whether the diagnosis of hemophilia was associated with protection against COVID-19 severity and other clinical outcomes. We found no significant difference in mortality (5.7% vs 4.3%, OR 1.3, 95% CI 0.7-2.4), in PwH compared to matched controls without hemophilia and having hemophilia was not a risk factor for death (OR 1.32, 95% CI 0.74-2.31). We did find that PwH were more likely to have moderate COVID-19 severity and to be hospitalized.[39] However, other markers of severity, including ICU admission and need for oxygen therapy was not different in PwH compared to controls. These findings are contrary to the findings of previous studies which suggested a milder course of COVID-19 in PwH, including a study from the Madrid Registry (n=345; PwH, 246)[20], case series from Iran (n=61; PwH, 42)[43] and Italy (n=13)[22] Although few case-reports have reported severe disease and mortality in PwH with cardiovascular disease, [22, 25] these studies were limited by small sample sizes and were not able to compare outcomes to similarly matched patients without hemophilia as we did in this study.

We postulated that PwH may be at decreased risk for VTE with COVID-19; however, we found the VTE incidence was similar for PwH and matched non-hemophilia controls (3.8% vs 2.9%, OR 1.3, 95%CI 0.6-2.7). This suggests that PwH with COVID-19 are not protected against VTE despite the hypocoagulable state of hemophilia. It is important to note is that the rates of VTE with COVID-19 in this study are lower than what has been previously reported in other studies (~30%). [1, 44] The reasons for this are not clear, however, we did not examine the VTE rates over time during the study period. The advent of SARS-CoV-2 therapeutic interventions, changes in anticoagulation practice, and SARS-CoV-2 vaccine may have contributed to lower VTE rates during the observational period. In addition, we were not able to access and review radiograph reports to identify individuals with VTE who were not coded with a VTE diagnosis. We also examined risk factors for VTE in PwH and found that a prior history of VTE and anticoagulation use increased the risk of an index-VTE event. This may be expected as those individuals being treated for a VTE would likely be identified to have an index-VTE.

Of all the comorbidities examined, we found only pulmonary disease as a risk for VTE in PwH.[45] Underlying lung pathology may be exacerbated by SARS-CoV-2 infection which in turn contributes

to local and systemic thrombosis.[13] Although anticoagulation thromboprophylaxis is commonly prescribed to hospitalized patients with COVID-19, providers may not routinely administer anticoagulation to PwH due to bleeding risk. Therefore, it was surprising to note that in our dataset the frequency of anticoagulation use was similar in PwH and non-hemophilia patients (15% vs 16%) during the index encounter. The benefit of anticoagulation in PwH could not be determined in this study as the VTE rate was not different between the two cohorts and there was no interaction found with hemophilia and anticoagulation, suggesting that anticoagulant use did not influence VTE rate. In contrast to the general population, we did not find an association between VTE and adverse COVID-19 outcomes in PwH (OR 0.57, 95%CI 0.03-2.93).[14] We speculate that thrombotic complications in PwH may be associated with endothelial dysfunction with the viral infection, and that it is less dependent on the procoagulant functions of FVIII and FIX.[4] Therefore, the deficiency of FVIII and FIX, regardless of its severity, may not offer significant benefit towards reducing thrombotic risk in the presence of vasculopathy.

While VTE rates did not differ between PwH and matched controls, non-CNS bleeding was increased in PwH (19% vs 5.9%, OR 3.7, 95%CI 2.5-5.6). Unlike VTE, non-CNS bleeding increased the odds of poor outcomes in PwH (OR 2.70, 95%CI 1.18-6.33). However, both anticoagulation and hemophilia therapy use did not increase (or decrease) the risk of COVID-19 severity. Of the comorbidities investigated, hepatitis C and liver disease were significantly associated with bleeding in PwH. This finding of increased bleeding might be expected in PwH, however, the influence of anticoagulation and hemophilia therapy factor on bleeding risk could not be determined in this study due to the small sample size and low event rate. This suggests that prevention of bleeding is critical in PwH with COVID-19, however additional studies are needed to better risk stratify PwH who are appropriate for anticoagulation prophylaxis and factor replacement.

We showed that PwH shared common risk-factors for COVID-19 adverse outcomes which have been identified in the general population.[1, 2, 6-9, 11, 12] These comorbidities included cardiovascular disease, liver disease, cancer, dementia, and renal disease. Other common risks such as obesity and diabetes were not demonstrated in PwH We showed that PwH shared common risk-factors for COVID-19 adverse outcomes which have been identified in the general population.[1, 2, 6-9, 11, 12] These comorbidities included

5.1 | Strengths and limitations

The major strength of this study is the large sample size of N3C database which enabled us to apply propensity-matching to estimate the independent effect of hemophilia on COVID-19 outcomes.[27] Since this registry is drawn from wide geographical distribution, it is representative of US population. We were able to use this representative sample to address questions of VTE and bleeding risk in a rare disease like hemophilia and its associations with severe COVID-19. However, the study has several limitations in addition to those that are inherent to the observational design. First, the source data for this study is derived from electronic medical records. It is subject to coding errors, accuracy and completeness of data, missing data, and variability in data entry among various healthcare systems.[46] Second, we were not able to examine the association between hemophilia severity (mild, moderate and severe) and disease outcomes. The current ICD-10 manual does not include hemophilia severity codes which limited our ability to characterize hemophilia severity.[36] Our data shows that only 10% of our study cohort received hemophilia therapy implying a larger fraction of PwH may have non-severe disease. This is difficult to explain as ~40% of PwH seen at tertiry care facilties have severe hemophilia. Since bleeding comborbidity adversely affected COVID-19 outcomes, and hemophilia severity directly affects bleeding phenotype, it is critical to have further studies to better understand this relationship. Third, caution should be applied while generalizing our findings to entire hemophilia population in US as we identified only ~5% (n=1,676) of national hemophilia population (n=~30,000). Therefoe, despite being the largest study so far, our finding may not be applicable to entire hemophilia population in US.[19] Furthermore, the cohort is subject to selection bias as it included only those individuals who sought medical care for COVID-19 at N3C participating sites and heterogeneity in care delivery among sites may influence observed outcomes. Forth, the limited historical data within the N3C platform may have resulted in missing hemophilia diagnoses if it were not pulled into lookback data and not included into the patient encounter. Lastly, we did not study the secular changes in pandemic due to lack of viral strain and vaccination data within N3C, which could have provided additional insights about lower event rates observed in our study. Despite these limitations, our analyses used a large sample that is most representative U.S. cohort of COVID-19 cases and controls to date.

In summary, this is the first comparative study that evaluated the outcomes of COVID-19 in PwH using a diverse sample size from the largest COVID-19 cohort from US. The study shows that hemophilia is not protective against COVID-19 adverse outcomes and VTE. We find that bleeding

comorbidity was associated with poor outcomes with COVID-19 in PwH. The management of COVID-19 in PwH needs careful assessments of bleeding and thrombotic risk and an ongoing investigation as the pandemic is transitioning towards an endemic state. Future studies are needed to better understand how to best use hemophilia therapeutics and anticoagulation therapy for optimal management of PwH with COVID-19.

Author contributions

Conceptualization and study design: AS; methodology: AS, CT, CO, LW; concept mapping: AS, CT CO; data-extraction: CO; data interpretation and writing: LW, AS, CT; study methodology, interpretation of analyses and manuscript writing: AS, CT, CO, LW, RS, EC.

CH: DIRECT contributions to the manuscript at the Consortial level [Consortial: clinical data model expertise; Consortial: data curation; Consortial: data integration; Consortial: data quality assurance; Consortial: funding acquisition; Consortial: governance; Consortial: critical revision of the manuscript for important intellectual content; Consortial: N3C Phenotype definition; Consortial: project evaluation; Consortial: project management; Consortial: regulatory oversight / administration]. All authors have read and approved the final manuscript and agree to the published version of the article.

Acknowledgements and funding support

N3C Attribution

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave covid.cd2h.org/enclave and supported by CD2H - The National COVID Cohort Collaborative (N3C) IDeA CTR Collaboration 3U24TR002306-04S2 NCATS U24 TR002306. This research was possible because of the patients whose information is included within the data from participating organizations (covid.cd2h.org/dtas) and the organizations and scientists (covid.cd2h.org/duas) who have contributed to the on-going development of this community resource (cite this https://doi.org/10.1093/jamia/ocaa196).

The study was supported by the Clinical and Translational Science Award grant funded from the National Institutes of Health (UL1TR002537) to University of Iowa

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the N3C program.

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave (covid.cd2h.org/enclave) and supported by NCATS U24 TR002306. This research was possible because of the patients whose information is included within the data from participating organizations: https://ncats-nih-gov.proxy.lib.uiowa.edu/n3c/resources/data-contribution/data-transfer-agreement-signatories and scientists who have contributed to the ongoing development of this community resource (doi.org/10.5281/zenodo.3979622). Authorship was determined using ICMJE recommendations.

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

We gratefully acknowledge the following core contributors to N3C:

Adam B. Wilcox, Adam M. Lee, Alexis Graves, Alfred (Jerrod) Anzalone, Amin Manna, Amit Saha, Amy Olex, Andrea Zhou, Andrew E. Williams, Andrew Southerland, Andrew T. Girvin, Anita Walden, Anjali A. Sharathkumar, Benjamin Amor, Benjamin Bates, Brian Hendricks, Brijesh Patel, Caleb Alexander, Carolyn Bramante, Cavin Ward-Caviness, Charisse Madlock-Brown, Christine Suver, Christopher Chute, Christopher Dillon, Chunlei Wu, Clare Schmitt, Cliff Takemoto, Dan Housman, Davera Gabriel, David A. Eichmann, Diego Mazzotti, Don Brown, Eilis Boudreau, Elaine Hill, Elizabeth Zampino, Emily Carlson Marti, Emily R. Pfaff, Evan French, Farrukh M Koraishy, Federico Mariona, Fred Prior, George Sokos, Greg Martin, Harold Lehmann, Heidi Spratt, Hemalkumar Mehta, Hongfang Liu, Hythem Sidky, J.W. Awori Hayanga, Jami Pincavitch, Jaylyn Clark, Jeremy Richard Harper, Jessica Islam, Jin Ge, Joel Gagnier, Joel H. Saltz, Joel Saltz, Johanna Loomba, John Buse, Jomol Mathew, Joni L. Rutter, Julie A. McMurry, Justin Guinney, Justin Starren, Karen Crowley, Katie Rebecca Bradwell, Kellie M. Walters, Ken Wilkins, Kenneth R. Gersing, Kenrick Dwain Cato, Kimberly Murray, Kristin Kostka, Lavance Northington, Lee Allan Pyles, Leonie Misquitta, Lesley

Cottrell, Lili Portilla, Mariam Deacy, Mark M. Bissell, Marshall Clark, Mary Emmett, Mary Morrison Saltz, Matvey B. Palchuk, Melissa A. Haendel, Meredith Adams, Meredith Temple-O'Connor, Michael G. Kurilla, Michele Morris, Nabeel Qureshi, Nasia Safdar, Nicole Garbarini, Noha Sharafeldin, Ofer Sadan, Patricia A. Francis, Penny Wung Burgoon, Peter Robinson, Philip R.O. Payne, Rafael Fuentes, Randeep Jawa, Rebecca Erwin-Cohen, Rena Patel, Richard A. Moffitt, Richard L. Zhu, Rishi Kamaleswaran, Robert Hurley, Robert T. Miller, Saiju Pyarajan, Sam G. Michael, Samuel Bozzette, Sandeep Mallipattu, Satyanarayana Vedula, Scott Chapman, Shawn T. O'Neil, Soko Setoguchi, Stephanie S. Hong, Steve Johnson, Tellen D. Bennett, Tiffany Callahan, Umit Topaloglu, Usman Sheikh, Valery Gordon, Vignesh Subbian, Warren A. Kibbe, Wenndy Hernandez, Will Beasley, Will Cooper, William Hillegass, Xiaohan Tanner Zhang. Details of contributions available at covid.cd2h.org/core-contributors

The following institutions whose data is released or pending:

Available: Advocate Health Care Network — UL1TR002389: The Institute for Translational Medicine (ITM) • Boston University Medical Campus — UL1TR001430: Boston University Clinical and Translational Science Institute • Brown University — U54GM115677: Advance Clinical Translational Research (Advance-CTR) • Carilion Clinic — UL1TR003015: iTHRIV Integrated Translational health Research Institute of Virginia • Charleston Area Medical Center — U54GM104942: West Virginia Clinical and Translational Science Institute (WVCTSI) • Children's Hospital Colorado — UL1TR002535: Colorado Clinical and Translational Sciences Institute • Columbia University Irving Medical Center — UL1TR001873: Irving Institute for Clinical and Translational Research • Duke University — UL1TR002553: Duke Clinical and Translational Science Institute • George Washington Children's Research Institute — UL1TR001876: Clinical and Translational Science Institute at Children's National (CTSA-CN) • George Washington University — UL1TR001876: Clinical and Translational Science Institute at Children's National (CTSA-CN) • Indiana University School of Medicine — UL1TR002529: Indiana Clinical and Translational Science Institute • Johns Hopkins University — UL1TR003098: Johns Hopkins Institute for Clinical and Translational Research • Loyola Medicine — Loyola University Medical Center • Loyola University Medical Center — UL1TR002389: The Institute for Translational Medicine (ITM) • Maine Medical Center — U54GM115516: Northern New England Clinical & Translational Research (NNE-CTR) Network • Massachusetts General Brigham — UL1TR002541: Harvard Catalyst • Mayo Clinic Rochester — UL1TR002377: Mayo Clinic Center for Clinical and Translational Science (CCaTS) •

Medical University of South Carolina — UL1TR001450: South Carolina Clinical & Translational Research Institute (SCTR) • Montefiore Medical Center — UL1TR002556: Institute for Clinical and Translational Research at Einstein and Montefiore • Nemours — U54GM104941: Delaware CTR ACCEL Program • NorthShore University HealthSystem — UL1TR002389: The Institute for Translational Medicine (ITM) • Northwestern University at Chicago — UL1TR001422: Northwestern University Clinical and Translational Science Institute (NUCATS) • OCHIN — INV-018455: Bill and Melinda Gates Foundation grant to Sage Bionetworks • Oregon Health & Science University — UL1TR002369: Oregon Clinical and Translational Research Institute • Penn State Health Milton S. Hershey Medical Center — UL1TR002014: Penn State Clinical and Translational Science Institute • Rush University Medical Center — UL1TR002389: The Institute for Translational Medicine (ITM) • Rutgers, The State University of New Jersey — UL1TR003017: New Jersey Alliance for Clinical and Translational Science • Stony Brook University — U24TR002306 • The Ohio State University — UL1TR002733: Center for Clinical and Translational Science • The State University of New York at Buffalo — UL1TR001412: Clinical and Translational Science Institute • The University of Chicago — UL1TR002389: The Institute for Translational Medicine (ITM) • The University of Iowa — UL1TR002537: Institute for Clinical and Translational Science • The University of Miami Leonard M. Miller School of Medicine — UL1TR002736: University of Miami Clinical and Translational Science Institute • The University of Michigan at Ann Arbor — UL1TR002240: Michigan Institute for Clinical and Health Research • The University of Texas Health Science Center at Houston — UL1TR003167: Center for Clinical and Translational Sciences (CCTS) • The University of Texas Medical Branch at Galveston — UL1TR001439: The Institute for Translational Sciences • The University of Utah — UL1TR002538: Uhealth Center for Clinical and Translational Science • Tufts Medical Center — UL1TR002544: Tufts Clinical and Translational Science Institute • Tulane University — UL1TR003096: Center for Clinical and Translational Science • University Medical Center New Orleans — U54GM104940: Louisiana Clinical and Translational Science (LA CaTS) Center • University of Alabama at Birmingham — UL1TR003096: Center for Clinical and Translational Science • University of Arkansas for Medical Sciences — UL1TR003107: UAMS Translational Research Institute • University of Cincinnati — UL1TR001425: Center for Clinical and Translational Science and Training • University of Colorado Denver, Anschutz Medical Campus — UL1TR002535: Colorado Clinical and Translational Sciences Institute • University of Illinois at Chicago — UL1TR002003: UIC Center for Clinical and Translational Science • University of Kansas Medical Center — UL1TR002366: Frontiers: University of Kansas Clinical and Translational Science Institute • University of Kentucky — UL1TR001998: UK Center

for Clinical and Translational Science • University of Massachusetts Medical School Worcester — UL1TR001453: The UMass Center for Clinical and Translational Science (UMCCTS) • University of Minnesota — UL1TR002494: Clinical and Translational Science Institute • University of Mississippi Medical Center — U54GM115428: Mississippi Center for Clinical and Translational Research (CCTR) • University of Nebraska Medical Center — U54GM115458: Great Plains IDeA-Clinical & Translational Research • University of North Carolina at Chapel Hill — UL1TR002489: North Carolina Translational and Clinical Science Institute • University of Oklahoma Health Sciences Center — U54GM104938: Oklahoma Clinical and Translational Science Institute (OCTSI) • University of Rochester — UL1TR002001: UR Clinical & Translational Science Institute • University of Southern California — UL1TR001855: The Southern California Clinical and Translational Science Institute (SC CTSI) • University of Vermont — U54GM115516: Northern New England Clinical & Translational Research (NNE-CTR) Network • University of Virginia — UL1TR003015: iTHRIV Integrated Translational health Research Institute of Virginia • University of Washington — UL1TR002319: Institute of Translational Health Sciences • University of Wisconsin-Madison — UL1TR002373: UW Institute for Clinical and Translational Research • Vanderbilt University Medical Center — UL1TR002243: Vanderbilt Institute for Clinical and Translational Research • Virginia Commonwealth University — UL1TR002649: C. Kenneth and Dianne Wright Center for Clinical and Translational Research • Wake Forest University Health Sciences — UL1TR001420: Wake Forest Clinical and Translational Science Institute • Washington University in St. Louis — UL1TR002345: Institute of Clinical and Translational Sciences • Weill Medical College of Cornell University — UL1TR002384: Weill Cornell Medicine Clinical and Translational Science Center • West Virginia University — U54GM104942: West Virginia Clinical and Translational Science Institute (WVCTSI)

Submitted: Icahn School of Medicine at Mount Sinai — UL1TR001433: ConduITS Institute for Translational Sciences • The University of Texas Health Science Center at Tyler — UL1TR003167: Center for Clinical and Translational Sciences (CCTS) • University of California, Davis — UL1TR001860: UCDavis Health Clinical and Translational Science Center • University of California, Irvine — UL1TR001414: The UC Irvine Institute for Clinical and Translational Science (ICTS) • University of California, Los Angeles — UL1TR001881: UCLA Clinical Translational Science Institute • University of California, San Diego — UL1TR001442: Altman Clinical and Translational Research Institute • University of California, San Francisco — UL1TR001872: UCSF Clinical and Translational Science Institute

Pending: Arkansas Children's Hospital — UL1TR003107: UAMS Translational Research Institute • Baylor College of Medicine — None (Voluntary) • Children's Hospital of Philadelphia — UL1TR001878: Institute for Translational Medicine and Therapeutics • Cincinnati Children's Hospital Medical Center — UL1TR001425: Center for Clinical and Translational Science and Training • Emory University — UL1TR002378: Georgia Clinical and Translational Science Alliance • HonorHealth — None (Voluntary) • Loyola University Chicago — UL1TR002389: The Institute for Translational Medicine (ITM) • Medical College of Wisconsin — UL1TR001436: Clinical and Translational Science Institute of Southeast Wisconsin • MedStar Health Research Institute — UL1TR001409: The Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS) • MetroHealth — None (Voluntary) • Montana State University — U54GM115371: American Indian/Alaska Native CTR • NYU Langone Medical Center — UL1TR001445: Langone Health's Clinical and Translational Science Institute • Ochsner Medical Center — U54GM104940: Louisiana Clinical and Translational Science (LA CaTS) Center • Regenstrief Institute — UL1TR002529: Indiana Clinical and Translational Science Institute • Sanford Research — None (Voluntary) • Stanford University — UL1TR003142: Spectrum: The Stanford Center for Clinical and Translational Research and Education • The Rockefeller University — UL1TR001866: Center for Clinical and Translational Science • The Scripps Research Institute — UL1TR002550: Scripps Research Translational Institute • University of Florida — UL1TR001427: UF Clinical and Translational Science Institute • University of New Mexico Health Sciences Center — UL1TR001449: University of New Mexico Clinical and Translational Science Center • University of Texas Health Science Center at San Antonio — UL1TR002645: Institute for Integration of Medicine and Science • Yale New Haven Hospital — UL1TR001863: Yale Center for Clinical Investigation• On behalf of N3C Consortium.

CONFLICT OF INTEREST

AS has received honoraria and served as institutional principal investigator for clinical studies from CSL Behring, Genentech, Pfizer, Bristol-Meier Squibb, Takeda and NIH.

CT has received honoraria and served as institutional principal investigator for clinical studies from Novartis, Global Blood Therapeutics, Forma Therapeutics, Genentech, Daiichi-Sankyo. CC has

received NIH/NCATS funding for N3C collaborative. LW, CO, EC, RS, and the N3C investigators declare no conflicts of interest.

References

1 Bennett TD, Moffitt RA, Hajagos JG, Amor B, Anand A, Bissell MM, Bradwell KR, Bremer C, Byrd JB, Denham A, DeWitt PE, Gabriel D, Garibaldi BT, Girvin AT, Guinney J, Hill EL, Hong SS, Jimenez H, Kavuluru R, Kostka K, Lehmann HP, Levitt E, Mallipattu SK, Manna A, McMurry JA, Morris M, Muschelli J, Neumann AJ, Palchuk MB, Pfaff ER, Qian Z, Qureshi N, Russell S, Spratt H, Walden A, Williams AE, Wooldridge JT, Yoo YJ, Zhang XT, Zhu RL, Austin CP, Saltz JH, Gersing KR, Haendel MA, Chute CG. The National COVID Cohort Collaborative: Clinical Characterization and Early Severity Prediction. *medRxiv*. 2021. 10.1101/2021.01.12.21249511.

2 Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021; **21**: 855. 10.1186/s12879-021-06536-3.

3 Leung JM, Sin DD. Smoking, ACE-2 and COVID-19: ongoing controversies. *Eur Respir J*. 2020; **56**. 10.1183/13993003.01759-2020.

4 Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care*. 2020; **24**: 360. 10.1186/s13054-020-03077-0.

5 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama*. 2020; **323**: 2052-9. 10.1001/jama.2020.6775.

6 Rajpal A, Rahimi L, Ismail-Beigi F. Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *J Diabetes*. 2020; **12**: 895-908. 10.1111/1753-0407.13085.

7 Sharafeldin N, Bates B, Song Q, Madhira V, Yan Y, Dong S, Lee E, Kuhrt N, Shao YR, Liu F, Bergquist T, Guinney J, Su J, Topaloglu U. Outcomes of COVID-19 in Patients With Cancer: Report From the National COVID Cohort Collaborative (N3C). *J Clin Oncol*. 2021; **39**: 2232-46. 10.1200/jco.21.01074.

8 Xu J, Xiao W, Liang X, Shi L, Zhang P, Wang Y, Wang Y, Yang H. A meta-analysis on the risk factors adjusted association between cardiovascular disease and COVID-19 severity. *BMC Public Health*. 2021; **21**: 1533. 10.1186/s12889-021-11051-w.

9 Ge J, Pletcher MJ, Lai JC. Outcomes of SARS-CoV-2 Infection in Patients With Chronic Liver Disease and Cirrhosis: A National COVID Cohort Collaborative Study. *Gastroenterology*. 2021; **161**: 1487-501.e5. 10.1053/j.gastro.2021.07.010.

10 Chung EYM, Palmer SC, Natale P, Krishnan A, Cooper TE, Saglimbene VM, Ruospo M, Au E, Jayanti S, Liang A, Jie Deng DJ, Chui J, Higgins GY, Tong A, Wong G, Teixeira-Pinto A, Hodson EM, Craig JC, Strippoli GFM. Incidence and Outcomes of COVID-19 in People With CKD: A

Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2021; **78**: 804-15. 10.1053/j.ajkd.2021.07.003.

11 Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, Gan H, Sun YL, Fu W, Li W, Liang HL, Cao YY, Yan Q, Cao C, Gao HY, Brüggen MC, van de Veen W, Sokolowska M, Akdis M, Akdis CA. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy*. 2021; **76**: 428-55. 10.1111/all.14657.

12 Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, Ross DW, Sharma P, Sakhiya V, Fishbane S, Jhaveri KD. Outcomes Among Patients Hospitalized With COVID-19 and Acute Kidney Injury. *Am J Kidney Dis*. 2021; **77**: 204-15.e1. 10.1053/j.ajkd.2020.09.002.

13 Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. 2020; **173**: 268-77. 10.7326/m20-2003.

14 Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. *Vasc Med*. 2021; **26**: 415-25. 10.1177/1358863x21995566.

15 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020; **18**: 1094-9. 10.1111/jth.14817.

16 Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020; **18**: 1023-6. 10.1111/jth.14810.

17 Vincent JL, Levi M, Hunt BJ. Prevention and management of thrombosis in hospitalised patients with COVID-19 pneumonia. *Lancet Respir Med*. 2022; **10**: 214-20. 10.1016/s2213-2600(21)00455-0.

18 Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. *N Engl J Med*. 2001; **344**: 1773-9. 10.1056/nejm200106073442307.

19 https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2021-09/table-2-factor.html; last accessed March 2022.

20 Álvarez Román MT, Butta Coll N, García Barcenilla S, Pérez González L, de la Plaza Collazo I, De la Corte Rodríguez H, Romero Garrido JA, Martín Salces M, Rivas Pollmar MI, Cebanu T, González-Zorrilla E, Acuña P, Monzón Manzano E, Rodríguez Merchán EC, Trelles Martínez R, Blanco Bañares MJ, Gutiérrez Alvariño M, Jiménez Yuste V. Registry of patients with congenital bleeding disorders and COVID-19 in Madrid. *Haemophilia*. 2020; **26**: 773-8. 10.1111/hae.14089.

21 Dorgalaleh A, Dabbagh A, Tabibian S, Baghaeipour MR, Jazebi M, Bahraini M, Fazeli S, Rad F, Baghaeipour N. Patients with Congenital Bleeding Disorders Appear to be Less Severely Affected by SARS-CoV-2: Is Inherited Hypocoagulability Overcoming Acquired Hypercoagulability of Coronavirus Disease 2019 (COVID-19)? *Semin Thromb Hemost*. 2020; **46**: 853-5. 10.1055/s-0040-1713435.

22 Coluccia A, Marchesini E, Giuffrida AC, Rivolta GF, Ricca I, Zanon E, Luciani M, De Cristofaro R, Coppola A, Rocino A. Addressing the impact of SARS-CoV-2 infection in persons with congenital bleeding disorders: The Italian MECCOVID-19 study. *Haemophilia*. 2021; **27**: e575-e8. 10.1111/hae.14331.

23 Pinto Pereira J, Hantson P, Gerard L, Wittebole X, Laterre PF, Lambert C, Hermans C. Management of COVID-19 Coagulopathy in a Patient with Severe Haemophilia A. *Acta Haematol*. 2021; **144**: 319-21. 10.1159/000510591.

24 Rivas-Pollmar MI, Álvarez-Román MT, Butta-Coll NV, Martín Salces M, García-Barcenilla S, Jiménez-Yuste V. Thromboprophylaxis in a patient with COVID-19 and severe hemophilia A on emicizumab prophylaxis. *J Thromb Haemost*. 2020; **18**: 2202-4. 10.1111/jth.14954.

25 Cui D, Zhang A, Liu A, Hu Q. Clinical findings in a patient with haemophilia A affected by COVID-19. *Haemophilia*. 2020; **26**: e214-e6. 10.1111/hae.14000.

26 Pipe SW, Kaczmarek R, Srivastava A, Pierce GF, Makris M, Hermans C. Management of COVID-19-associated coagulopathy in persons with haemophilia. *Haemophilia*. 2021; **27**: 41-8. 10.1111/hae.14191.

27 Johnson SR, Tomlinson GA, Hawker GA, Granton JT, Feldman BM. Propensity Score Methods for Bias Reduction in Observational Studies of Treatment Effect. *Rheum Dis Clin North Am*. 2018; **44**: 203-13. 10.1016/j.rdc.2018.01.002.

28 Haendel MA, Chute CG, Bennett TD, Eichmann DA, Guinney J, Kibbe WA, Payne PRO, Pfaff ER, Robinson PN, Saltz JH, Spratt H, Suver C, Wilbanks J, Wilcox AB, Williams AE, Wu C, Blacketer C, Bradford RL, Cimino JJ, Clark M, Colmenares EW, Francis PA, Gabriel D, Graves A, Hemadri R, Hong SS, Hripscak G, Jiao D, Klann JG, Kostka K, Lee AM, Lehmann HP, Lingrey L, Miller RT, Morris M, Murphy SN, Natarajan K, Palchuk MB, Sheikh U, Solbrig H, Visweswaran S, Walden A, Walters KM, Weber GM, Zhang XT, Zhu RL, Amor B, Girvin AT, Manna A, Qureshi N, Kurilla MG, Michael SG, Portilla LM, Rutter JL, Austin CP, Gersing KR. The National COVID Cohort Collaborative (N3C): Rationale, design, infrastructure, and deployment. *J Am Med Inform Assoc*. 2021; **28**: 427-43. 10.1093/jamia/ocaa196.

29 Bradwell KR, Wooldridge JT, Amor B, Bennett TD, Anand A, Bremer C, Yoo YJ, Qian Z, Johnson SG, Pfaff ER, Girvin AT, Manna A, Niehaus EA, Hong SS, Zhang XT, Zhu RL, Bissell M, Qureshi N, Saltz J, Haendel MA, Chute CG, Lehmann HP, Moffitt RA. Harmonizing units and values of quantitative data elements in a very large nationally pooled electronic health record (EHR) dataset. *J Am Med Inform Assoc*. 2022; **29**: 1172-82. 10.1093/jamia/ocac054.

30 Maier C, Kapsner LA, Mate S, Prokosch HU, Kraus S. Patient Cohort Identification on Time Series Data Using the OMOP Common Data Model. *Appl Clin Inform*. 2021; **12**: 57-64. 10.1055/s-0040-1721481.

31 Hripcsak G, Duke JD, Shah NH, Reich CG, Huser V, Schuemie MJ, Suchard MA, Park RW, Wong IC, Rijnbeek PR, van der Lei J, Pratt N, Norén GN, Li YC, Stang PE, Madigan D, Ryan PB. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform*. 2015; **216**: 574-8.

32 Pfaff ER, Haendel MA, Kostka K, Lee A, Niehaus E, Palchuk MB, Walters K, Chute CG. Ensuring a safe(r) harbor: Excising personally identifiable information from structured electronic health record data. *J Clin Transl Sci*. 2022; **6**: e10. 10.1017/cts.2021.880.

33 National COVID Cohort Collaborative Phenotype Data Acquisition. https://github.com/National-COVID-Cohort-Collaborative/Phenotype_Data_Acquisition [Last accessed Oct, 2022).

34 Montagnier L. AIDS, hepatitis and hemophilia. *J Thromb Haemost*. 2004; **2**: 514-5. 10.1111/j.1538-7933.2004.00666.x.

35 Kulkarni R, Soucie JM, Evatt B. Renal disease among males with haemophilia. *Haemophilia*. 2003; **9**: 703-10. 10.1046/j.1351-8216.2003.00821.x.

36 ICD10 diagnostic and billing codes. codes.https://www.icd10data.com/.

37 Aledort LM, Evatt BL, Lusher JM, Brownstein AP. HIV and hemophilia. *J Thromb Haemost*. 2007; **5**: 607-10. 10.1111/j.1538-7836.2007.02371.x.

38 Transmission of hepatitis C virus infection associated with home infusion therapy for hemophilia. *MMWR Morb Mortal Wkly Rep*. 1997; **46**: 597-9.

39 A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020; **20**: e192-e7. 10.1016/s1473-3099(20)30483-7.

40 Komen JJ, Belitser SV, Wyss R, Schneeweiss S, Taams AC, Pajouheshnia R, Forslund T, Klungel OH. Greedy caliper propensity score matching can yield variable estimates of the treatment-outcome association-A simulation study. *Pharmacoepidemiol Drug Saf*. 2021; **30**: 934-51. 10.1002/pds.5232.

41 Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf*. 2012; **21 Suppl 2**: 69-80. 10.1002/pds.3263.

42 Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011; **173**: 676-82. 10.1093/aje/kwq433.

43 Karimi M, Haghpanah S, Shahsavani A. Prevalence and clinical features of COVID-19 in Iranian patients with congenital coagulation disorders. *Blood Transfus*. 2020; **18**: 413-4. 10.2450/2020.0223-20.

44 Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*. 2020; **142**: 114-28. 10.1161/circulationaha.120.046702.

45 Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med*. 2021; **9**: 909-23. 10.1016/s2213-2600(21)00095-3.

46 Cook JA, Collins GS. The rise of big clinical databases. *Br J Surg*. 2015; **102**: e93-e101. 10.1002/bjs.9723.

Figure Legends:

Figure 1: Flow diagram showing COVID-19 study cohort selection-persons with hemophilia (cases) and propensity matched cohort of patients without hemophilia (controls).

Figure 2: Univariate analyses of persons with hemophilia (PwH) with COVID-19 cohort showing risk-factors for adverse outcomes at index encounter. Figure A shows association with hemophilia and VTE related variables while Figure B shows association with systemic comorbidities.

Figure 3: Univariate analyses of persons with hemophilia (PwH) with COVID-19 showing risk factors for venous thromboembolism (VTE) and bleeding present at COVID-19 index encounter that were extracted from historical "lookback data". Figure A shows hemophilia and VTE related variables while figure B shows systemic comorbidities.

Table 1: Patient characteristics of 1: 3 propensity score-matched cohorts of male patients with and without hemophilia and COVID-19.

Patient characteristic	N	With Hemophilia, N = 300[1]	No Hemophilia, N = 900[1]	p-value[2]
Patient demographics				
Age at index encounter, years[$]	1200	39 (23, 58)	40 (23, 60)	0.7
Age category, years	1200			>0.9
<18		54 (18%)	160 (18%)	
18-29		53 (18%)	158 (18%)	
30-49		74 (25%)	220 (24%)	
50-64		67 (22%)	201 (22%)	
>= 65		52 (17%)	161 (18%)	
Weight, Kg	692	86 (67, 106)	87 (69, 107)	0.3
BMI, Kg/m2	553	27 (23, 35)	27 (23, 33)	0.6
Overweight/obesity (>30 kg/m^2)	571	91 (59%)	256 (61%)	0.7
Insurance	219			0.7
Insured (public/private)		74 (24.6%)	145 (16.1%)	
Missing		226 (75.3%)	755 (83.8)	
Race[$]	1200			0.7
Black or AA		45 (15%)	146 (16%)	
White		213 (71%)	634 (70%)	
Other/unknown		32 (14.3%)	120 (13.3%)	
Ethnicity[$]	1200			>0.9
Hispanic or Latino		36 (12%)	107 (12%)	
Missing/Unknown		30 (10%)	89 (9.9%)	
Not Hispanic or Latino		234 (78%)	704 (78%)	
Matched comorbidities				
Coronary artery disease[$]	1200	36 (12%)	124 (14%)	0.5
Heart failure[$]	1200	28(9.3%)	106(12%)	0.3
Hypertension[$]	1200	110 (37%)	359 (40%)	0.3
Cerebrovascular disease[$]	1200	20 (6.7%)	58 (6.4%)	0.9
Diabetes, complicated[$]	1200	43 (14%)	154 (17%)	0.3
Diabetes, uncomplicated[$]	1200	63 (21%)	219 (24%)	0.3
Dementia[$]	1200	8 (2.7%)	27 (3.0%)	0.8
Pulmonary disease[$]	1200	61 (20%)	194 (22%)	0.7
Malignancy/cancer[$]	1200	33 (11%)	97 (11%)	>0.9

Liver disease, mild[$]	1200	42 (14%)	120 (13%)	0.8
Liver disease, mod to severe[$]	1200	19 (6.3%)	48 (5.3%)	0.6
Substance abuse[$]	1200	21 (7.0%)	63 (7.0%)	>0.9
Tobacco smoking (current) [$]	1200	22 (7.3%)	69 (7.7%)	>0.9
Charlson comorbidity index	1200			>0.9
0		150 (50%)	462 (51%)	
1 to 2		73 (24%)	202 (22%)	
3 to 4		26 (8.7%)	78 (8.7%)	
5+		51 (17%)	158 (18%)	
Unmatched comorbidity				
Renal disease	1200	25 (8.3%)	129 (14%)	**0.007**
Hepatitis C	1200	45 (15%)	59 (6.6%)	**<0.001**
HIV infection	1200	15 (5.0%)	42 (4.7%)	0.9
Venous thromboembolism	1172	20 (6.9%)	35 (4.0%)	0.4
Bleeding-CNS	1200	11 (3.7%)	14 (1.6%)	0.035
Bleeding-non-CNS	1200	102 (34%)	103 (11%)	**<0.001**
Heme arthrosis-joint bleeding	1200	47 (16%)	<10	**<0.001**
Hemophilia and anticoagulation therapy				
Hemophilia therapeutics**	1200	30 (10%)	<10[#]	**<0.001**
Anticoagulation therapy***				
Pre-index encounter	1200	17 (5.7%)	75 (8.3%)	0.2
During index-encounter	1200	45 (15%)	147 (16%)	0.6

BMI: Body mass index; overweight, BMI>25-30 kg/m^2 and obesity, BMI > 30 kg/m^2; CNS, central nervous system;
$indicates baseline matching variables for propensity score matching for cohorts with and without hemophilia;
**hemophilia therapy includes plasma derived and recombinant (standard and extended half-life) factor VIII or IX concentrates, bypassing agents (NovoSeven, Kcentra and Prothrombin complex concentrates) and non-factor therapy with emicizumab;
#received bypassing agents (NovoSeven) for bleeding control
***Anticoagulation therapy included direct oral anticoagulants (DOACs), low molecular weight heparin (LMWH), unfractionated heparin (UFH) and warfarin

Table 2: Outcomes of COVID-19 (during index encounter and or within 30 days of initiation of index encounter) in a 1: 3 propensity score-matched cohorts of male patients with and without hemophilia.

Outcomes	N	With Hemophilia, N = 300[1]	No Hemophilia, N = 900[1]	Odds Ratio, 95% CI	p-value[2]
COVID-19 severity	1200				0.014
Mild		198 (66%)	679 (75%)	0.6 (0.5-0.8)	**0.002**
Moderate		77 (26%)	161 (18%)	1.6 (1.2-2.1)	**0.004**
Severe		<10 (<3%)*	21 (2.3%)	-	
30-day- all cause mortality		17 (5.7%)	39 (4.3%)	1.3 (0.7-2.4)	0.3
Hospitalization	1200	121 (40%)	269 (30%)	1.6 (1.2-2.0)	**0.001**
30-day-Hospitalization	1114	51 (18%)	126 (15%)	1.2 (0.9-1.7)	0.2
ICU admission	1200	<10 (<3%)*	28 (3.1%)	-	>0.9
ICU length of stay, days	37	34 (25, 66)	18 (10, 34)	-	0.074
Hypoxia (O_2 saturation <90%)	1200	25 (8.3%)	58 (6.4%)	1.3 (0.8-2.1)	0.3
ECMO	1200	<10 (<3%)*	<10 (<3%)*	-	NS
Bleeding-CNS	1200	<10 (<3%)*	<10 (<3%)*	-	NS
Bleeding-non-CNS	1200	57 (19%)	53 (5.9%)	3.7 (2.5-5.6)	**<0.001**
Venous thromboembolism**	1173	11 (3.8%)	26 (2.9%)	1.3 (0.6-2.7)	0.4
Anticoagulation therapy-during index encounter	1200	45 (15%)	147 (16%)	0.9 (0.6-1.3)	0.6

[1] Statistics presented: n (%); median (IQR)
[2] Statistical tests performed: Fisher's exact test; Wilcoxon rank-sum test
Abbreviations: CI: confidence interval; ICU: intensive care unit; DVT: Deep venous thrombosis; PE: pulmonary embolism; ECMO: extracorporeal membranous oxygenation; NS: Not significant; CNS: central nervous system
* The N3C Download committee reviewed and granted an appeal for this manuscript to report cell numbers as low as 10 (instead of the normal threshold of 20). Cell counts <10 were not reported to protect the privacy of individuals.
** Venous thromboembolism includes deep venous thrombosis and pulmonary embolism

Table 3: Results of multivariate model predicting adverse outcomes, severe COVID-19 and 30-day-all-cause-mortality, for the 1: 3 propensity score-matched cohorts of patients with COVID-19 with hemophilia with COVID-19 and without hemophilia and COVID-19.

Characteristic	Odds Ratio[1]	95% CI[1]	p-value
Hemophilia	1.32	0.74, 2.31	0.3
Age, years at index visit	1.03	1.02, 1.05	**<0.001**
Ethnicity			
Hispanic or Latino	—	—	
Missing/Unknown	1.47	0.52, 4.47	0.5
Not Hispanic or Latino	0.66	0.29, 1.74	0.4
Heart failure	3.53	1.97, 6.31	**<0.001**
Hypertension	1.94	1.00, 3.88	0.054
Liver disease, moderate to severe	7.05	3.69, 13.4	**<0.001**
CNS-bleeding	5.39	1.70, 16.0	**0.003**
Substance abuse	0.51	0.19, 1.22	0.2

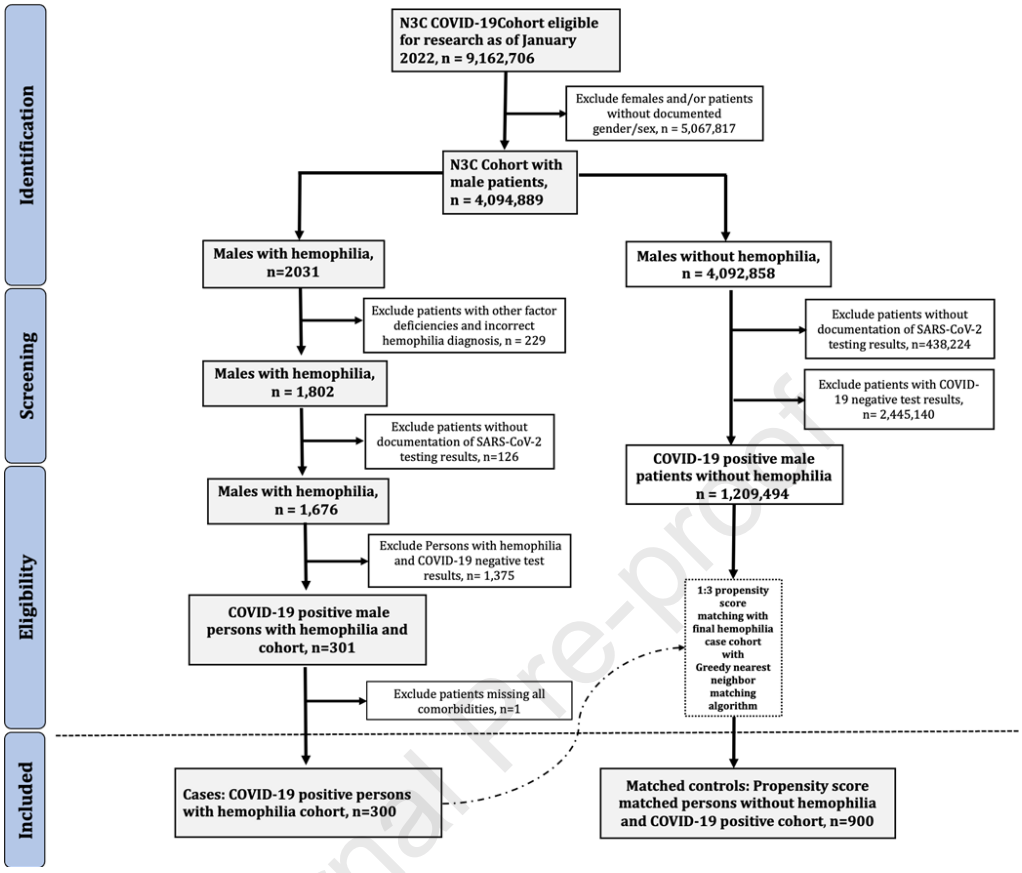
[1]OR = Odds Ratio, CI = Confidence Interval

Table 4: Multivariate analyses of propensity-score matched cohorts of patients with and without hemophilia showing hemophilia was not a risk-factor for venous thromboembolism and bleeding: A. Risk factors for venous thromboembolism; B. Risk factors for bleeding

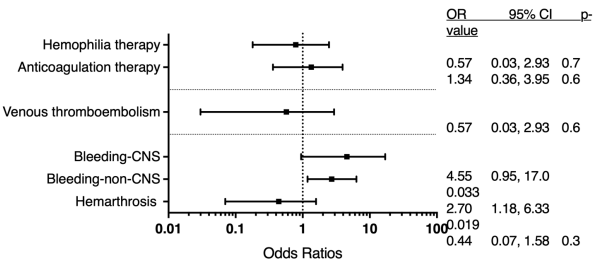
	Venous thromboembolism			**Bleeding outcome**		
Characteristic	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Hemophilia	1.14	0.44, 2.67	0.8	4.70	2.98, 7.48	**<0.001**
Age at index visit, years	1.02	1.01, 1.04	**0.006**	1.01	1.00, 1.02	0.011
Liver disease, Mild	-	-	-	1.59	0.84, 2.89	0.14
Liver disease, moderate to severe	-	-	-	4.26	2.07, 8.85	**<0.001**
Hemophilia therapy	-	-	-	0.91	0.19, 3.12	0.9
Anticoagulation (pre-Index)	3.95	1.54, 9.37	**0.003**	2.38	1.12, 4.80	0.018
Hemophilia * Pre-Index_Anticoagulant use	1.94	0.31, 10.5	0.4	0.54	0.12, 2.12	0.4

[1] OR = Odds Ratio, CI = Confidence Interval

Figure 1: Flow diagram showing study COVID-19 cohort selection-persons with hemophilia (cases) and propensity matched cohort of patients without hemophilia (matched controls).

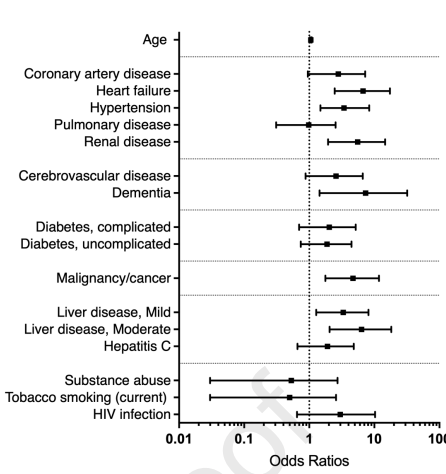


A. Risk for severe COVID-19 outcomes in PwH:
Hemophilia and VTE related variables



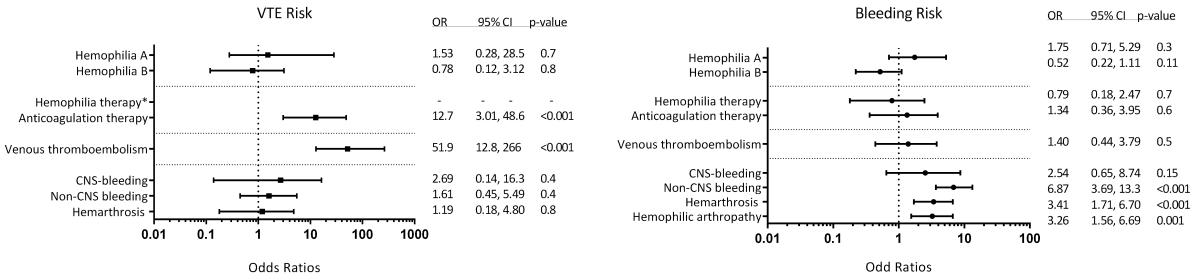
	OR	95% CI	p-value
Hemophilia therapy			
Anticoagulation therapy	0.57	0.03, 2.93	0.7
	1.34	0.36, 3.95	0.6
Venous thromboembolism	0.57	0.03, 2.93	0.6
Bleeding-CNS			
Bleeding-non-CNS	4.55	0.95, 17.0	0.033
Hemarthrosis	2.70	1.18, 6.33	0.019
	0.44	0.07, 1.58	0.3

B. Risk for severe COVID-19 outcomes in PwH:
Systemic comorbidities



	OR	95% CI	p-value
Age	1.06	1.03, 1.09	<0.001
Coronary artery disease			
Heart failure	3.30	1.20, 8.30	0.014
Hypertension	6.00	2.22, 15.4	<0.001
Pulmonary disease	3.42	1.49, 8.37	0.005
Renal disease	0.98	0.31, 2.54	>0.9
Cerebrovascular disease	5.55	1.95, 14.7	<0.001
Dementia			
Diabetes, complicated	2.58	0.88, 6.65	0.062
Diabetes, uncomplicated	7.36	1.44, 32.1	0.009
Malignancy/cancer	1.88	0.74, 4.47	0.2
Liver disease, Mild	2.03	0.70, 5.17	0.2
Liver disease, Moderate			
Hepatitis C	4.71	1.77, 11.8	0.001
Substance abuse	3.34	1.28, 8.13	0.01
Tobacco smoking (current)			
HIV infection	6.36	2.05, 18.2	<0.001
	0.91	0.66, 4.84	0.2
	0.53	0.03, 2.73	0.5
	0.50	0.03, 2.58	0.5
	2.99	0.65, 10.3	0.11

A. Risk for VTE and Bleeding outcomes in PwH with COVID-19: Hemophilia and VTE related variables



B. Risk for VTE and Bleeding outcomes in PwH with COVID-19: Systemic comorbidities